A Theoretical Application of Click Reaction to Obtain Heterotricyclic Compounds

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ABSTRACT

1,3–dipolar cycloaddition reactions are the ones which have been widely used for many years in the synthesis of five–membered heterocyclic compounds, take an important place in synthetic organic chemistry. Even though they are very useful, they have been used in the synthesis of significant natural products since early 1980s. In this study, we examined intramolecular synthesis of tricyclic products with the Click Reaction mechanisms, theoretically. The use of azide substituted five and six membered cyclic starting materials and provided obtaining heterotricyclic compounds in one step. Derivatization was performed by changing the ring size (m) and varying substitüent (R). The reaction coordinates for all reactions were formed upon finding intermediates and transition states.

INTRODUCTION

Cycloaddition reaction is a type of addition reactions classified under chemical pericyclic reactions (1). If ring systems are formed as a result of addition reactions, cycloaddition is possible. In cycloaddition reactions, two molecules with π–bonds get into reaction and as a result two new σ bonds are formed and transformed into a cyclic structure. The driving power in the reaction is the fact that σ bonds are more stable than π bonds. With the use of substituents which change in the reaction new compounds with cyclic structure could be synthesized. For this reason, cycloaddition reactions have a wide spectrum of application (2).

Azide-alkyne 1,3-dipolar cycloaddition reaction is known as “Huisgen Cycloaddition Reaction” (3). Sharpless called the reaction of coming together of small units as “Click Chemistry” (CC). Azide-alkyne, on the other hand, described 1,3 dipolar cycloaddition reaction as the best example of Click reaction (4).

Click reaction is a method which is often used for single-step synthesis of bicyclic or tricyclic compounds. There are bicyclic or tricyclic hetero rings in the content of many medicines. Therefore, synthesis of heterocyclic structures are very important for pharmaceutical sciences. In addition to that, it has a wide use in areas such as medicinal inventions (5), bio conjugation, polymer and material science (6), supramolecular chemistry (7) and tagging of deoxyribonucleic acid (8).

1,2,3-triazole compounds are interesting connecting units because they are stable against metabolic degradation and they can connect to biomolecular targets as they are able to make hydrogen bonds (9). Although 1,2,3 triazoles show some different biological activity, they do not exist in the nature. The triazolic compounds have undeniable importance for the medical chemistry. There are many triazole derivatives mentioned in the literature. Contrary to other azoheterocylics, 1,2,3 triazole rings are not protonated at pH physiological pH level because of low alkalinity.

The purpose of computational chemistry is to understand chemical reactions and processes in a better way. Today, many properties of molecules can be calculated without making any experiment with the help of theoretical computations. These calculations could be easily made even for compounds that are not obtained or not possible to obtain up to now, and could never be obtained under real conditions and the desired result are achieved. Theoretical data could be informative. It could guide the experimental study and it can be used together with experimental study in a comparative way. In this way, the reliability of experimental studies and data increases and the method is supported. For this reason, the interest in theoretical studies is increasing day by day (10).

In this study, a theoretical application of the Click Chemistry was performed in order to gain information about the reaction mechanism of the formation of a tricyclic hetero compound in one step and without using a catalyst.

This study has importance from the viewpoint of the realization of Click reaction without catalyst. It aims at theoretical synthesis in one step of three rings fused together as a result of intramolecular Click reaction.

COMPUTATIONAL METHOD

Geometric optimizations of all structures is realized first through MM2 method and then half-empiric PM3 Self-Consistent Field Molecular Orbital (SCMFO) method. Higher levels of geometric optimization is achieved with use of RHF and B3LYP/6-31G (d,p). None

of the normal mode analysis for each compound resulted in negative frequency in either of three calculation methods.

In addition to the calculations, the stability of the compounds are analysed in solvent environment (THF). This is practically important because the execution of experimental conditions in laboratory in solvent environment is important in terms of interaction between solvent and the solute and their stabilities. Self-consistent SCRF model is used generally in order to explain the level of chemical reactions in the environment. In this model, microscopic data on the interaction between biomolecules and surrounding molecules is neglected. Instead of that, small THF clusters are used in order to model some of the properties of the solvent. Effects of the solvent are analysed with SCRF method and Polarizable Continuum Model (PMC) is also used.

During the studies, Gaussian03W modelling program, the most widespread package program of today's computational chemistry, is used. GaussView5.0 graphical interface program is used in order analyse the calculations made with Gaussian. Calculation are made with the help of a HP420WS desktop computer with Intel Xeon ® CPU E5–1650 v2Q 3.50 GHz X 12 64–bit 48 GIB. Calculations are carried out with high performance server systems (work station) over the LINUX operating system.

RESULTS AND DISCUSSION

The purpose of this study is to theoretically analyse the synthesis mechanism of tricyclic products with intramolecular Click reaction. The use of cyclic azide starting materials and the capability of azide group for 1,3-dipolar addition makes possible the production of heterocyclic products in single step. The beginning molecules, which are designed in the study, are analysed under four different groups. While making this grouping, first of all, aromatic and aliphatic groups are separated and then later, alkyl group ($–CH_3$) is added to these structures and in this way molecular chain is continued to be extended. Derivatization is made with by substituents (R) by changing ring sizes (n,m).

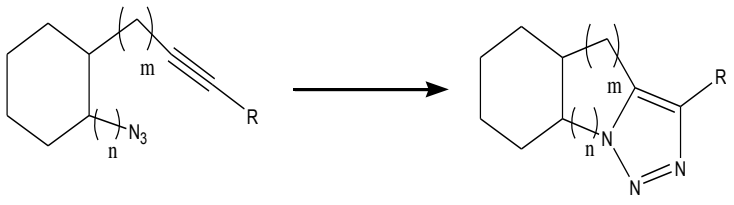


Figure 1. General Illustration of Click reaction

This thesis study has importance from the viewpoint of the realization of Click reaction without catalyser. It aims at theoretical synthesis in one step of three rings fused together as a result of intramolecular Click reaction.

With the help of computer program called GaussView5.0, the geometries of the molecules are prepared and the resulting simulations of the molecules are examined. Related theoretical calculations are made with the help of package program Gaussian03W.

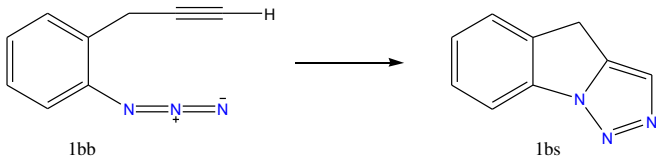
The molecular reactants that are designed with GausView5.0 are represented by the expression “beginning (b)”; while the ending products of the reaction by “result (s) and the molecules formed as a result of the widening of terminal alkyne by (g).

Three dimensional (3D) forms of molecules are created, geometry and energy of reactant and ending molecules (with geometrical optimization) and reaction by products and transition states (TS) are specified. In determining the transitional states, vibrational frequency values and intrinsic reaction coordinate (IRC) calculations are used. The same calculations are made for 1.group molecules (shown as 1a_ and 1a_g) in solvent environment (tetrahydrofuran, THF).

Geometric Optimization of Molecules and Energy Results

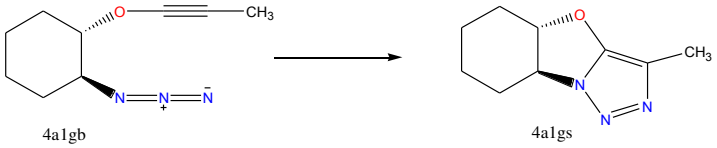
Molecular geometry, which is created before starting the optimisation with GausView5.0 is an unstable structure. With geometric optimization, the most stable structure is achieved for a molecule; that is to say, the structure stable with minimum energy is found. During the geometric optimization, bond lengths, bond angles and dihedral angles are optimised and their values are changed. The energy level is expressed in unit of Hartree (atomic unit, a.u.).

As a result of the use of basic sets, frequency calculations are valid over the potential energy surface of the molecule in regions called Stationary Points where the energy is minimum. That is why, frequency calculations are based on optimized geometries. Having all values positive in frequency calculations, is an expression of the fact that there is at least one minimum over the potential energy surface of the structure, which is optimized. That is why, optimizing (opt) and vibration (freq/vib) calculation operations can be inserted to the program as a single operation under a single command “opt freq” and there is no need to make separate calculations. Selection of the method for molecule calculations (DFT/B3LYP) and selection of basic set 6-31 g(d,p) are important. The right method and basic set are selected by trials.

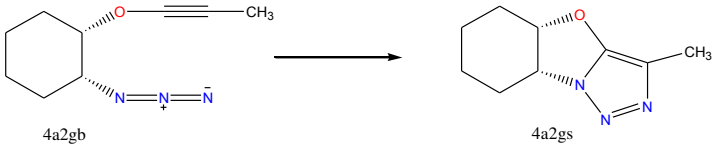


1bb 1bs

Figure 2. Expected Click reaction of 1b molecule with an aromatic ring



4a1gb 4a1gs



4a2gb 4a2gs

Figure 3. Expected Click reactions of 4ag methyl substituted alkyne molecule with an aliphatic ring

Scan calculations (approximation of atoms) are made after the optimisation of reactants. The approximation of internal and terminal carbon (C) and nitrogen (N) atoms of Alkyne and azide groups are calculated one by one for each reactant. Scan calculation and graphics of 1bb, a reactant in gas phase, are provided in Figure 4 and Figure 5.

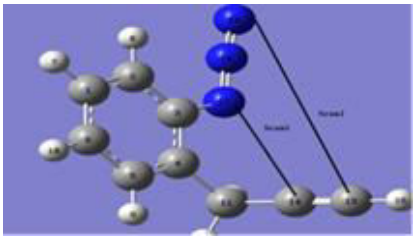


Figure 4. Method used in SCAN calculation of a molecule.

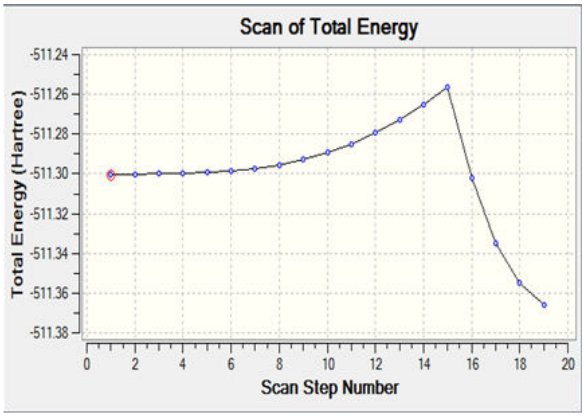


Figure 5. Graphic of scan calculation for 1bb in gas phase.

At point 15 of the SCAN graphic shown in the Figure, TS is observed. Whether the expected closing in the molecule takes place or not; if so, how it is closed and its energy, bonding point and the situation at points before bonding are observed as a result of this calculation. The points before bonding, bonding points and points after the bonding are determined by SCAN graphics and after that TS calculations are made for these points. Vibration value is important for TS calculations. It can be seen that, closing is as stronger as the level of the negativeness of this value. The observation of TS at a single point reveals that reaction takes place in single step. As a result of calculations at TS point, which is designated, energy and vibration values are found out.

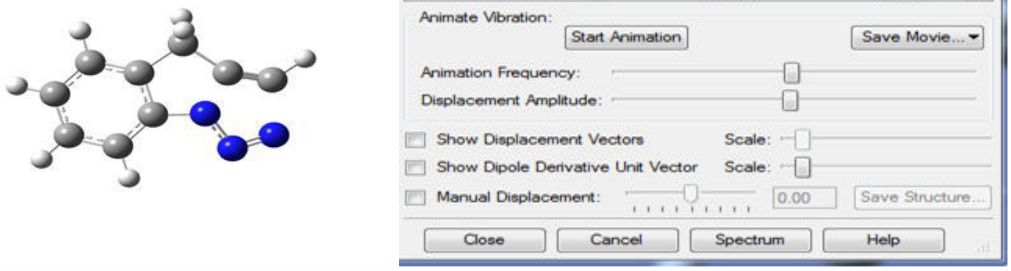


Figure 6. The geometric structure and vibration value at TS15 step of 1b molecule calculated in gas phase.

After energy is calculated for reactants at TS, energy of the product is calculated. In Table 1, you can see the optimized structures of reactants and products at DFT/B3LYP theoretical level by using the basic set of 6-31g (d,p).

Table 1. Optimized structures of reactants in gas phase and products at DFT/B3LYP theoretical level by using 6-31g(d,p) basic set.

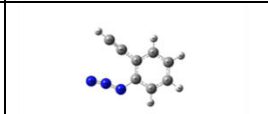
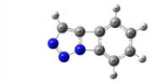
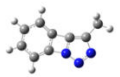
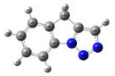
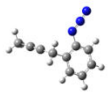
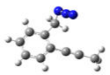
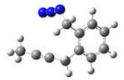
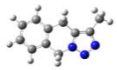
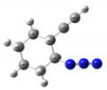
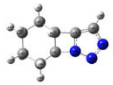
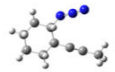
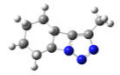
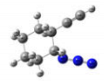
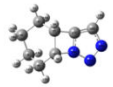
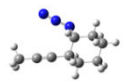
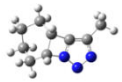
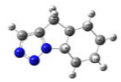
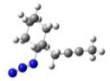
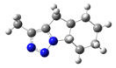
Name of the reactant	Optimized reactant structure	m	n	R	Name of the Products	Optimized product structure	Name of the reactant	Optimized reactant structure	m	n	R	Name of the Products	Optimized product structure
1ab		0	0	H	1as		1agb		0	0	$-CH_3$	1ags	
1bb		1	0	H	1bs		1bgb		1	0	$-CH_3$	1bgs	
1cb		0	1	H	1cs		1cgb		0	1	$-CH_3$	1cgs	
1db		1	1	H	1ds		1dgb		1	1	$-CH_3$	1dgs	
2a1b		0	0	H	2a1s		2a1gb		0	0	$-CH_3$	2a1gs	
2a2b		0	0	H	2a2s		2a2gb		0	0	$-CH_3$	2a2gs	
2b1b		1	0	H	2b1s		2b1gb		1	0	$-CH_3$	2b1gs	

Table 1. Optimized structures of reactants in gas phase and products at DFT/B3LYP theoretical level by using 6-31g(d,p) basic set. (continued)

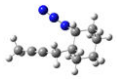
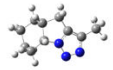
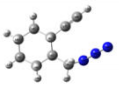
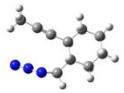
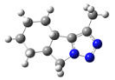
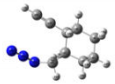
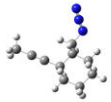
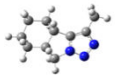
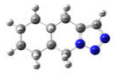
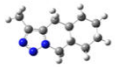
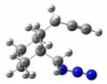
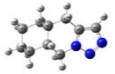
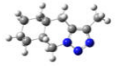
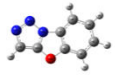
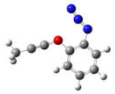
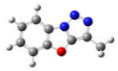
Name of the reactant	Optimized reactant structure	m	n	R	Name of the Products	Optimized product structure	Name of the reactant	Optimized reactant structure	m	n	R	Name of the Products	Optimized product structure
2b2b		1	0	H	2b2s		2b2gb		1	0	$-CH_3$	2b2gs	
2c1b		0	1	H	2c1s		2c1gb		0	1	$-CH_3$	2c1gs	
2c2b		0	1	H	2c2s		2c2gb		0	1	$-CH_3$	2c2gs	
2d1b		1	1	H	2d1s		2d1gb		1	1	$-CH_3$	2d1gs	
2d2b		1	1	H	2d2s		2d2gb		1	1	$-CH_3$	2d2gs	
3ab		O	0	H	3as		3agb		O	0	$-CH_3$	3ags	

Table 1. Optimized structures of reactants in gas phase and products at DFT/B3LYP theoretical level by using 6-31g(d,p) basic set. (continued)

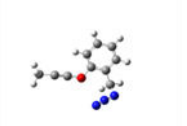
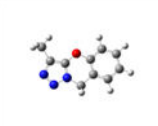
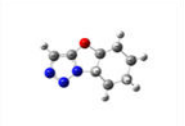
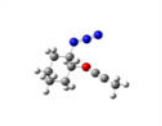
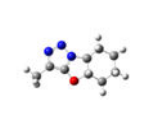
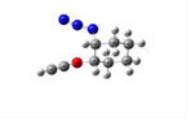
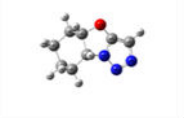
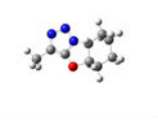
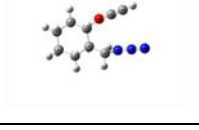
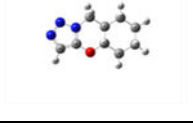
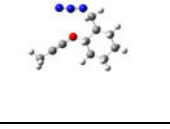
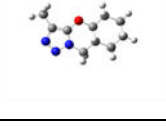
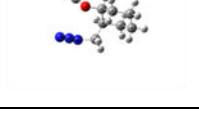
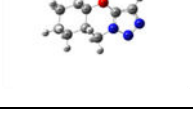
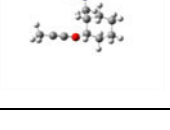
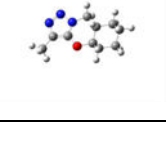
Name of the reactant	Optimized reactant structure	m	n	R	Name of the Products	Optimized product structure	Name of the reactant	Optimized reactant structure	m	n	R	Name of the Products	Optimized product structure
3bb		O	1	H	3bs		3bgb		O	1	$-CH_3$	3bgs	
4a1b		O	0	H	4a1s		4a1gb		O	0	$-CH_3$	4a1gs	
4a2b		O	0	H	4a2s		4a2gb		O	0	$-CH_3$	4a2gs	
4b1b		O	1	H	4b1s		4b1gb		O	1	$-CH_3$	4b1gs	
4b2b		O	1	H	4b2s		4b2gb		O	1	$-CH_3$	4b2gs	

Table 2. Optimized structures of reactants in solvent phase and products at DFT/B3LYP theoretical level by using 6-31g(d,p) basic set.

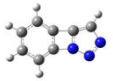
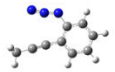
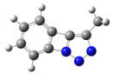
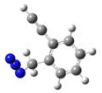
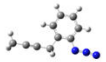
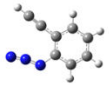
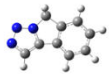
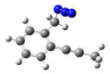
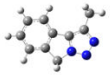
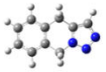
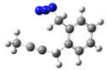
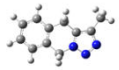
Name of the reactant	Optimized reactant structure	m	n	R	Name of the Products	Optimized product structure	Name of the reactant	Optimized reactant structure	m	n	R	Name of the Products	Optimized product structure
1a_b		0	0	H	1a_s		1a_gb		0	0	$-CH_3$	1a_gs	
1b_b		1	0	H	1b_s		1b_gb		1	0	$-CH_3$	1b_gs	
1c_b		0	1	H	1c_s		1c_gb		0	1	$-CH_3$	1c_gs	
1d_b		1	1	H	1d_s		1d_gb		1	1	$-CH_3$	1d_gs	

Chart 1: E_a and ΔH reaction values of molecules calculated in gas and solvent phase (THF) at theoretical level by using 6-31g(d,p) set.

Reaction	$E_{reactant}$ (a.u)	E_{TS} (a.u)	$E_{product}$ (a.u)	E_a (kj/mol)	ΔH (kj/mol)	Reaction	$E_{reactant}$ (a.u)	E_{TS} (a.u)	$E_{product}$ (a.u)	E_a (kj/mol)	ΔH (kj/mol)
1a	-472.0051	-471.9015	-471.9856	272.00	51.20	**1ag**	-511.3174	-511.2287	-511.3101	232.88	19.17
1b	-511.3002	-511.2599	-511.3946	105.81	-247.85	**1bg**	-550.6284	-550.5854	-550.7184	112.90	-236,30
1c	-511.2997	-511.2626	-511.3963	97.41	-253.62	**1cg**	-550.6290	-550.5885	-550.7201	106.33	-239.18
1d	-550.6082	-550.5744	-550.7211	88.74	-296.42	**1dg**	-589.9370	-589.8980	-590.0446	102.40	-282.50
2a1	-475.6338	-475.5440	-475.6370	235.77	-8.40	**2a1g**	-514.9458	-514.8696	-514.9604	200.06	-38.33
2a2	-475.6323	-475.5490	-475.6572	218.70	-65.38	**2a2g**	-514.9448	-514.8749	-514.9805	183.52	-93.73
2b1	-514.9525	-514.8941	-515.0255	153.33	-191.66	**2b1g**	-554.2619	-554.2157	-554.3487	121.30	-227.90
2b2	-514.9291	-514.8925	-515.0283	96.09	-260.45	**2b2g**	-554.2579	-554.2174	-554.3516	106.33	-246.01
2c1	-514.9279	-514.8891	-515.0235	101.87	-251.00	**2c1g**	-554.2566	-554.2141	-554.3465	111.58	-236.03
2c2	-514.9420	-514.8875	-515.0248	143.09	-217.40	**2c2g**	-554.2566	-554.2126	-554.3479	115.52	-239.71
2d1	-554.2436	-554.2067	-554.3577	96.88	-299.57	**2d1g**	-593.5714	-593.5302	-593.6812	108.17	-288.28
2d2	-554.2396	-554.2082	-554.3535	82.44	-299.05	**2d2g**	-593.5682	-593.5326	-593.6768	93.47	-285.13
3a	-547.1753	-547.1350	-547.2788	105.81	-271.74	**3ag**	-586.5031	-586.4601	-586.6027	112.90	-261.50
3b	-586.4889	-586.4458	-586.6082	113.16	-313.22	**3bg**	-625.8165	-625,7689	-625,9319	124.97	-302.98
4a1	-550.8146	-550.7744	-550.9060	105.55	-239.97	**4a1g**	-590.1398	-590.0949	-590.2293	117.89	-234.98
4a2	-550.8132	-550.7706	-550.9110	111.85	-256.77	**4a2g**	-590.1399	-590.0989	-590.2343	107.65	-247.85
4b1	-590.1241	-590.0944	-590.2453	77.98	-318.21	**4b1g**	-629.4526	-629.4268	-629.5687	67.74	-304.82
4b2	-590.1220	-590.0866	-590.2412	92.94	-313.49	**4b2g**	-629.4522	-629.3893	-629.5647	165.14	-295.37
1a_	-471.9943	-471.9092	-471.9855	223.43	23.10	**1a_g**	-511.3230	-511.2352	-511.3204	230.52	6,83
1b_	-511.3083	-511.2675	-511.4073	107.12	-259.93	**1b_g**	-550.6363	-550,5870	-550.7300	129.44	-246.27
1c_	-511.3082	-511.2711	-511.4096	97.41	-266.23	**1c_g**	-550.6363	-550.5955	-550.7321	107.12	-251.52
1d_	-550.6157	-550.5798	-550.7348	94.26	-312.70	**1d_g**	-589.9443	-589.9037	-590.0573	106.60	-296.68

$E_a = E_{TS} - E_{reactant}$
$\Delta H = E_{product} - E_{reactant}$ 1 Hartree or1 a.u (atomic unit) = 2625,5 kj/mol

When graphics of the reactions are drawn, it is seen that at top point reaction takes place in single step. In Figure7, you can see graphic of reaction mechanism for 1b molecule.

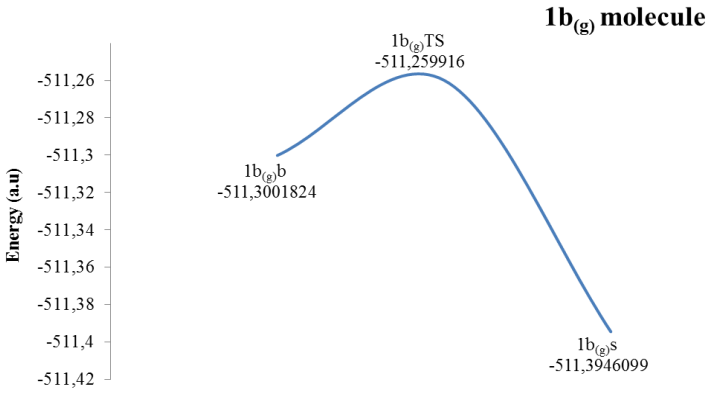


Figure 7: Graphic of reaction mechanism for 1b molecule in gas phase

Results of IRC Calculations

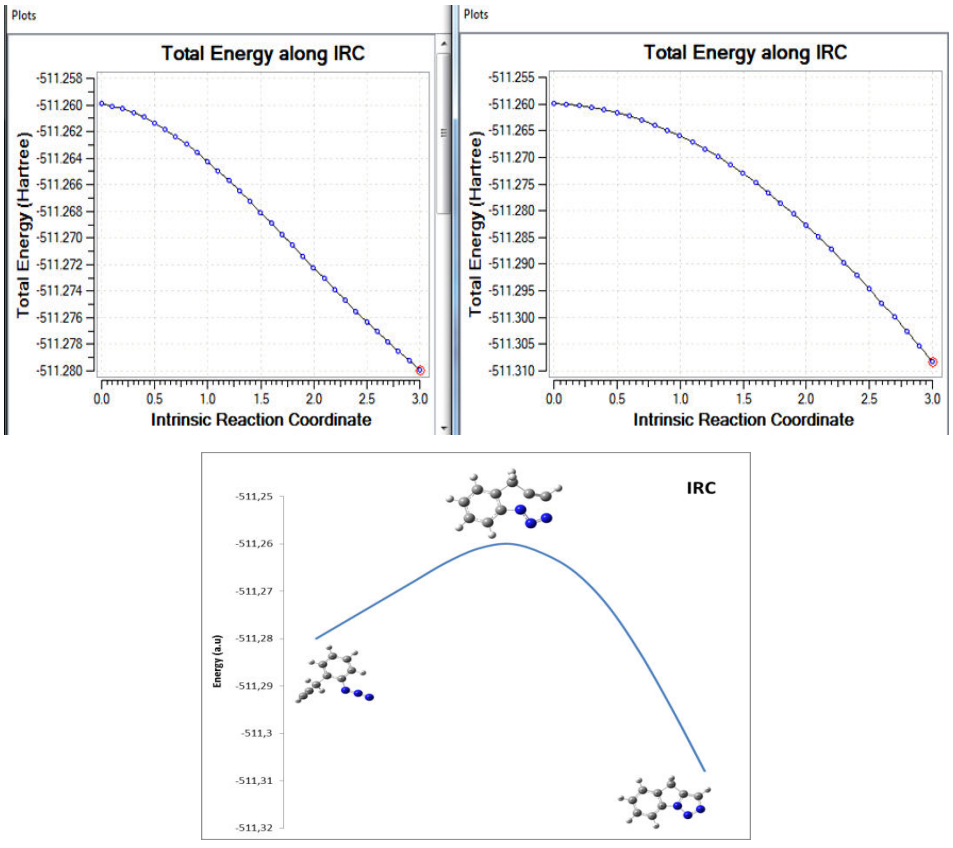


Figure 8: Graphic of reaction mechanism of IRC Analysis for molecule 1b calculated in gas phase by B3LYP/6-31G (d) method.

In this study which is thought to have importance from the viewpoint of the realization of Click reaction without catalyser, three ring-compounds fused together because of intramolecular Click reaction are theoretically synthesised in one step.

The beginning molecules, which are designed in the study, are analysed under four different groups. While making this grouping, first of all, aromatic and aliphatic groups are separated and then later, alkyl group ($–CH_3$) is added to these structures and in this way molecular chain is continued to be extended (from 1a to 2d2) The beginning molecules, 3rd and 4th groups, are derived with oxygen and the chain is extended (from3a to 4b2).

Moreover, steric effects of new molecules that are obtained by substituting hydrogen instead of methyl in all 4 beginning groups (from1ag to 4d2), enable us to study the stability, how E_a and $\Delta H'$ are changed, from a different perspective. The calculations are made also for 1st group molecules in solvent phase (from1a_d to 1d_g) in order to study the effects of the solvent; and thermodynamic properties in solvent phase (THF, a strong solvent) and gas phase are compared. In this way, azide-alkyne cycloaddition within the molecule and derivatives of 1,2,3-triazole and 1,2,3- triazole oxazine, which have different ring sizes, are synthesized and reaction mechanism of the compounds are theoretically studied.

Comparison of Stability of Starting Molecules

The optimized structures of the starting molecules are reached with the help of geometric optimization. When we look at the energy values of these structures, molecules can be evaluated under different groups.

Molecules of 1bb and 1cc, which are from Group1 molecules calculated in gas phase, are two structures with the same closed formula. When the beginning energy is considered, the molecule formed with chain extension by alkyne, 1bb is more stable, with a little difference, than the molecule formed with chain extension by azide, 1cb. For methyl substituted alkyne molecule calculated in gas phase, 1cgb structure, which is formed with chain extension by azide is more stable than 1bgb, which is formed with chain extension by alkyne.

In molecules from Group 1 calculated in solvent phase, 1b_b structure is much less stable than 1c_b structure while the stability of methyl substituted alkyne 1b_gb and the stability of 1c_gb structure are equal. When gas phase and solvent phase are compared, it is observed that molecules calculated in solvent phase are more stable and that, as a result of calculations made in SCRF solvent method using THF, solvent environment increases the stability by decreasing the beginning energy of the reactant, tough to a limited extent.

Group 2 type molecules are molecules that have aliphatic 6C rings. Conformer structure of cyclohexane should be taken into account. Conformers and isomers of cyclohexane and substitute cyclohexane (branched) have a very important place among the Cyclic (ring) compounds because, they can get to positions with very low energy in terms of bond strain and torsional strain and they can form very stable structures. Cyclohexane has several conformations.

Of these conformations, chair conformation is the most stable structure with lowest energy. That is why, for beginning molecules chair form is preferred. Axial and equatorial hydrogens are very important for stereoisomerism. Axial means that it is right-angled to the four carbon atoms which are on the same plane while equatorial means it is on a similar plane with four hydrogen atoms which are on the same plane. Derivatisation of substituents in cyclohexane is very important at just this point. According to bonding condition, product's geometric structure and stability is determined by whether the substituents are positioned as axial-axial/equatorial-equatorial or axial-equatorial/equatorial-axial. On the other hand, it is well known fact that conformations, which keep large substituent groups in equatorial position among cis/trans isomers, whether these are cis or trans isomers, have higher levels of energy.

In this study, 1st structures of molecules with aliphatic cycles are drawn as trans (substituents in equatorial-equatorial positions) and 2nd structure are drawn as cis (substituents in axial-equatorial position). For example, when 2a1b and 2a2b optimized structures are examined, it is seen that first structure is in trans position while second structure is in cis position.

When we look at the beginning energies in relation to cis/trans isomerism of 2nd group molecules calculated in gas phase, we can examine their stabilities among themselves. It is observed that 2a1b structure, whose 2a1b and 2a2b isomers are in trans position, is more stable compared to 2a2b structure. Again calculations show that 2a1gb isomer, which has methyl substituted alkyne, is more stable compared to 2a2gb isomer. 2b1b, 2b2b, 2c1b and 2c2b molecules within 2nd group have same structure isomerism with the same closed formula. Among these structures, most stable one is 2b1b, which has chain extension to the alkyne side and which is trans.

When we compare these structures among themselves, we see that as of 2b structures, trans 2b1b is more stable than cis 2b2b; as of 2c structures, cis 2c2b is more stable than trans 2c1b.

Again, 2b1gb, 2b2gb, 2c1gb and 2c2gb molecules with methyl substituted alkyne within 2nd group have same structure isomerism with the same closed formula. Among these structures, most stable one is 2b1gb, which has chain extension to the alkyne side and which is in trans position. As their energies are equal, 2c1gb and 2c2gb are also equal in terms of stability and cis/trans isomerism does not have much effect. When 2b structures are analysed among themselves, we see that trans 2b1gb is more stable than cis 2b2gb. As of 2d group molecules, trans 2d1b is more stable than cis 2d2b and trans 2d1gb with methyl substituted alkyne is more stable than cis 2d2gb.

Since 3rd group molecules do not have same closed formula, it is not possible to make any comment with regard to the comparison of their stability.

In gas phase, 4th group molecules are evaluated in a similar way with 2nd group molecules. When 4a1b and 4a2b molecules are compared, we see that they have same closed formula; trans 4a1b is more stable. Just the opposite of this is observed in 4ag molecule which has methyl substituted alkyne. Cis 4a2gb is more stable. Among the 4b1b and 4b2b molecules, trans 4b1b structure is more stable than cis 4b2b structure. Among methyl substituted alkyne molecules, trans 4b1gb molecule is more stable than cis 4b2gb isomer.

Comparison of the Stability of the Products Formed as a Result of Reaction

When the optimized structures and energy levels of the products are compared as a result of calculations made, it is possible to explain how and to what extend the steric effects of derivatisation and the size of the rings formed affect the stability.

When 1st group molecules calculated in gas phase are evaluated, it is observed that ring size change with chain extension. Of the 1bs and 1cs ending molecules with same closed formula, 1cs is more stable. When molecules with methyl substituted alkyne in gas phase are observed, we see 1cgs structure as more stable. In solvent phase, 1c_s is more stable than 1b_s while among molecules with methyl substituted alkyne, 1c_gs is more stable than 1b_gs.

When 2nd group molecules are observed, 2a2s is more stable than 2a1s. 2a2gs with methyl substituted alkyne is more stable than 2a1gs. 2b1s, 2b2s, 2c1s and 2c2s are molecules which have same closed formula. 2b2s is the most stable one among these structures. Moreover, when these structure are compared among themselves, it is seen that 2b2s is more stable than 2b1s and 2c2s is more stable than 2c1s. When structures with methyl substituted alkyne are evaluated, 2b2gs is the most stable one. 2b2gs is more stable than 2b1gs and 2c2gs is more stable than 2c1gs. Among 2d1s and 2d2s structures, 2d1s is more stable, while 2d1gs is most stable one within the structures with methyl substituted alkyne.

Of 4th group molecules, when 4a1s and 4a2s are evaluated, 4a2s is more stable. Among 4b molecules, 4b1s ending molecule is more stable than 4b2s ending molecule. Within the 4th group molecules with methyl substituted alkyne, 4a2gs is more stable than 4a1gs while 4b1gs is more stable than 4b2gs.

In order to explain the thermodynamic properties of Click chemistry reaction mechanism, E_a and ΔH values are also calculated for reactions that are theoretically studied in an environment without a catalyst.

Comparison of E_a s, which are necessary for Ring Closure

When we look at Chart1, E_a value gives us information on several issues. It is known that as the E_a value decreases, the reaction takes place faster, because there is an inversely proportional relationship between reaction's rate constant and E_a. When the reactions in gas phase are observed, it is seen that the reaction with the lowest E_a is the reaction where 4b1g molecule is formed while the reaction with highest E_a is the reaction where 1a molecule is formed. For 1st group molecules studied in solvent phase, the reaction forming 1d_ has highest E_a while the reaction forming 1a_g has lowest E_a.

When ending molecules formed with Click reactions are observed in groups, it is seen that their ring sizes and geometrical positions change. These ring have 6–4–5, 6–5–5, 6–6–5 structures. The analysis of molecular reactions shows that Ea increases or decreases depending on chain extension, derivatisation and whether the structure is aromatic or aliphatic. In this sense, evaluation can be made from different perspectives.

When the groups are studied one by one, it is observed that the energy of the activation decreases as the size of the ring increases. In fact, this is an expected situation, because it is known that the structure which is expected to close in the easiest and fastest way is the reaction that forms 6-membered ring, and that the most difficult and the slowest reaction, which could even be inconclusive is the reaction that forms 4-membered ring. When the Ea s of the molecules, which do not contain methyl group but with which chain extension is made with that group, are studied, it can be said that as chain is extended, Ea decreases, that is to say, the reaction gets faster.

For example, among the reactions that were studied in gas phase, the reaction with lowest activation energy, that is, the fastest reaction is the one forming 1d molecule. The reaction with highest activation energy is the reaction forming the ending molecule which have a 4-membered ring in addition to triazole ring. These results show that when we extend

the chain in the beginning molecule, the steric effect changes Ea. The results of the calculations show that as the chain is extended, Ea decreases and reaction gets faster.

If we put the activation energies of 1st group molecules in order, we can see is as following: $E_{a1d} < E_{a1c}$, $E_{a1b} < E_{a1a.}$ The same situation is observed in Ea results with methyl substituted alkyne (-CCCH3). But, the opposite result is seen in Eas of some other reactions. For example, Ea of the structure that will form 5-membered ring is lower than Ea of the structure that will form 5-membered ring. In this group of molecules derived with oxygen formation of 5-membered ring is faster. This situation is observed in another way for 4th group molecules. $E_{a4b1} < E_{a4a1}$ and Ea4b2< $E_{a4a2,}$ this situation has the same effect as chain extension that we have mentioned. But the situation is different with 4rd group Eas which have methyl substituted alkyne: $E_{a4b1g} < E_{a4a1g}$ and $E_{a4b2g} > E_{a4a2g.}$ In this point, it should be taken into account from where the chain extension is made; and from where and how the groups with aliphatic rings are connected.

Geometric situation is very important for structures with same closed formula in terms of the reaction's progress. When Eas is compared for 1c and 1b in gas phase: $E_{a1c} < E_{a1b}$. That is to say, the energy barrier is higher for reaction in which chain is extended in alkyne side. The same situation is observed for Ea of 1b_g and 1c_g for which terminal alkyne is extended. There is no change in this situation when we observe solvent phase. 5-membered ring structure, which is formed with the extension of chain on azide side, whether it is in gas phase or in solvent phase, has lower activation energy. Hence, the reaction takes place faster.

There are geometrical isomers in 2nd group, because there are structure with same closed formula in addition to aliphatic ring structures. In this group, 2b, which will form 5-membered ring after reaction, has lowest Ea. When we examine all Eas one by one, we see that 2a2 has lower activation energy compared to 2a1. The calculations show that within the 2b and 2c structures, which have same closed formula, among 2bs, 2b2 has a lower Ea while among 2cs 2c1 has lower Ea. In 2d structures, which give 6 membered ring, 2d2 has a lower Ea, that is to say, its reaction takes place faster. The same results observed for structures with methyl substituted alkyne.

In group 4, Ea is lower for 4a1 and 4a2. While the situation is same for 4b1g with methyl substituted alkyne, Ea of 4a2g is lower than Ea of 4a1g.

The existence of a difference between the Ea in gas phase and Ea in solvent phase is an important, noteworthy situation. When Eas in 1st group are observed, it is seen Eas are increasing for all structures, other than the structures that will form 4 membered rings. This situation stems from polarity of the solvent.

When all structures are compared among themselves, Eas of the reactions that will produce 4 membered rings decrease in structures with methyl substituted alkyne.

Moreover, Ea decreases in structures with methyl substituted alkyne when 2b1 and 2b1g; 2c2 and 2c2g; 4a2 and 4a2g; 4b1 and 4b1g are compared. The steric effect plays an important role in this situation.

Comparison of ΔH calculated from the energy differences of statrting and final molecules.

That the reaction, where 1a and 1ag are formed in gas phase and 1a_ and 1a_g are formed in solvent phase, is endothermic while all others are exothermic is a fact that draws attention at first glance. When we look at all other reactions forming 4-membered ring, (2a1, 2a2, 2a1g and 2a2g) although they are exothermic, energy levels are very low. These molecules are either endothermic or with very low energy because their 4 membered rings have high ring strain. This situation stemming from ring strain shows that reactants are more stable compared to products.

When we observe the ring size of molecules formed after reactions we see that as the ring size increases, more heat is released. Reaction becomes more exothermic. For example, in gas phase, 2d1 reaction is more exothermic than 2b1 reaction by 108 kj/mol. In a similar way, for molecules with methyl substituted alkyne, reaction becomes more exothermic when rings gets bigger. However, for molecules with same closed formula, which are different isomers, reactions' ΔH differs because of the effects of cis-trans isomer and steric effect over the ending molecule.

Reactions in molecules with methyl substituted alkyne have lower energy compared to the ones with terminal hydrogen. For example, 3a reaction is more exothermic than 3ag reaction by 10.52 kj/mol. But there are three reactions that are exceptions to this situation: 2a1 and 2a2g; 2b1 and 2b1g; 2c1 and 2c1g. Normally, it is expected that they are less exothermic for molecules with methyl substituted alkyne. But they are observed as being more exothermic.

When we look at the calculations made in gas phase in Chart1, without taking into account the structures containing 4-membered rings, we can conclude that the most exothermic reaction is the reaction where 4b1 molecule is formed.

On the other hand, the fact that reactions are less exothermic in solvent phase could be explained by polarity of the solvent. Most exothermic reaction is 1d_ reaction where 6-membered rings are formed.

This paper aimed at explaining Click reaction mechanism where derivatives of triazole with different sizes of rings is synthesized in an environment without a catalyst. The study has found out the influence of steric affect over product stability; geometric positioning of ending molecules stemming from the differences between conformers and thermodynamic differences between rings of different sizes, which are synthesised with chain extension. In addition to that solvent affect is also analysed.

Since structures with one hetero ring or more hetero rings are used as the beginning material in many scientific areas such as polymer, medicines, biochemistry, this study could change the perspectives in many areas. Thermodynamic values of molecules which are theoretically synthesised with intramolecular Click reaction and the reaction mechanism, which is explained, could help the enlightenment of many new molecules.

The fact that it is carried out without a catalyst is of great importance for pharmacology. Especially, for triazole which is preferred as a pharmaceutically active compound, there will be no need to remove copper from the new synthesized medicines.

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